Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 17-32 are pending in the application, with claims 17, 24, 26, 28 and 30 being the independent claims. Claim 34 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 17, 19, 24, 26, 28, 30 and 31 are sought to be amended. Support for the amended claims can be found throughout the specification, for example, at page 24, line 10, through page 30, line 27, and in the claims as originally filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Claim Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 34 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. *See* Paper No. 10, page 2. It is noted that claim 34 recites "The method of claim 32," and that claim 32 is directed to a composition. *See* Paper No. 10, page 2. Claim 34 has been canceled, thereby rendering this rejection moot.

II. Claim Rejections Under 35 U.S.C. § 103

Claims 17, 18, 20-30 and 32 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 94/23756. *See* Paper No. 10, page 2. Applicants respectfully traverse this rejection.

Claims 17, 18, 20, 21 and 22 are directed to antisense oligonucleotides which are complementary to an NTP mRNA sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1. Claim 24 is directed to a ribozyme comprising a target sequence which is complementary to an NTP mRNA sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1. Claims 26 and 28 are directed to oligodeoxynucleotides that form one or more triple stranded regions with the coding region of AD7c-NTP DNA, wherein said oligodeoxynucleotides have the sequence 3'X5'-L-5'X3', or 5'X3'-L-3'X-5', wherein X comprises an AD7c-NTP nucleic acid sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1, and wherein L represents an oligonucleotide linker or a bond. Claim 30 is directed to a ribonucleotide external guide nucleic acid molecule, comprising a 10-mer nucleotide sequence corresponding to nucleotides 150-1139 of SEQ ID NO:1 fused to a 3'NCCA nucleotide sequence, wherein N is a purine. Claims 23, 25, 27, 29 and 32 are directed to pharmaceutical compositions comprising the antisense oligonucleotide of claim 17, the ribozyme of claim 24, the oligodeoxynucleotide of claim 26, the oligodeoxynucleotide of claim 28, and the ribonucleotide of claim 30, respectively.

In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference

teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). The teaching or suggestion to make the claimed combination must be found in the prior art, not in Applicants' disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants respectfully submit that a person of ordinary skill in the art would not have been motivated to modify the disclosure of WO 94/23756. Therefore, a *prima facie* case of obviousness cannot be established with respect to the present claims.

WO 94/23756 includes a sequence referred to as "AD10-7" and depicted in Fig. 16R. The Examiner has provided, along with the Office Action, a sequence alignment comparing the nucleotide sequence of SEQ ID NO:1 of the present application ("Qy") to the nucleotide sequence of AD10-7 from WO 94/23756 ("Db"). Between nucleotides 150 and 1139 of SEQ ID NO:1, there are 69 places where the sequences do not match, referred to herein as "positions of non-identity."

In addition, WO 94/23756 indicates that the nucleotide sequences of the antisense molecules and ribozymes set forth therein should be selected from regions that are non-homologous to the nucleotide sequence of the related molecule, pancreatic thread protein (PTP). For example, it is stated that:

> sequence analysis of an NTP cDNA clone shows that NTP contains sequences which are nonhomologous to PTP DNA sequences (*see* Figure 9). Thus, the NTP antisense oligonucleotides of the present invention may be RNA or DNA which is complementary to and stably hybridizes with such sequences which are specific for an NTP. Use of an oligonucleotide complementary to this region allows for the selective hybridization to NTP mRNA and not to mRNA specifying PTP.

WO 94/23756 at page 48, lines 6-12. With respect to ribozymes, WO 94/23756 states that: "preferred targets for NTP ribozymes are the nucleotide sequences which are not

homologous with PTP sequences." *Id.* at page 52, lines 24-25. A person of ordinary skill in the art, in making the antisense compositions of WO 94/23756, would have therefore been discouraged from selecting nucleotide sequences of AD10-7 that are homologous to PTP.

There is nothing in WO 94/23756 that would have motivated a person of ordinary skill in the art to make antisense oligonucleotides, ribozymes, triple helix forming oligonucleotides or ribonucleotide external guide nucleic acid molecules that include nucleotide sequences that are complementary to or that correspond to sequences specifically located between nucleotides 150 and 1139 of SEQ ID NO:1. In fact, WO 94/23756 would have discouraged the use of several regions found between nucleotides 150 and 1139 of SEQ ID NO:1 due to their homology with sequences found in PTP. It is also stated in WO 94/23756 that "[p]referred antisense oligonucleotides bind to the 5'-end of the AD10-7 mRNA." *See* WO 94/23756 at page 48, lines 19-20. This statement would have also directed persons of ordinary skill in the art *away* from sequences located between nucleotides 150 and 1139 of SEQ ID NO:1. Moreover, selecting a nucleic acid sequence from AD10-7 that includes any one of the 69 positions of non-identity would have resulted in a molecule that falls outside the scope of the present claims.

In sum, there is nothing in WO 94/23756 that would have motivated one of ordinary skill in the art to specifically select a nucleotide sequence from AD10-7 that falls within nucleotides 150 and 1139 of SEQ ID NO:1, and either: (a) does not include one of the 69 positions of non-identity, or (b) contains the correct nucleotide(s) at the positions of non-identity. Therefore, a *prima facie* case of obviousness cannot be established.

The Examiner stated that:

> WO 94/23756 indicates at page 56 and 85 that a deposit of the AD10-7-DH1 was made to the ATCC under accession number 69262 which is the source of the errored sequence in WO 94/23756 and the "corrected" sequence of the instant application (see page 5 of the instant application).

Paper No. 10, page 3. The Examiner's position, therefore, appears to be that the biological material used to determine the sequences of AD10-7 (from WO 94/23756) and SEQ ID NO:1 (from the present application) are the same, and that the differences between the two sequences is due to errors in the sequencing process rather than differences in the biological material that was used to determine the respective sequences.

The reference to ATCC deposit No. 69262 in the present specification at page 5, lines 11-12, simply indicates that clone AD10-7, set forth in WO 94/23756, was deposited in DH1 cells at the ATCC. The specification does not indicate that SEQ ID NO:1 was determined by sequencing this particular clone. In fact, the biological material from which SEQ ID NO:1 was determined is distinct from the biological material that was used to obtain the nucleotide sequence set forth in WO 94/23756. According to WO 94/23756, a human brain Alzheimer's disease cDNA library was screened with a 416 bp DNA fragment corresponding to nucleotides 235-650 of the rat PTP cDNA ("O18"). *See* WO 94/23756 at page 67, lines 1-18, and at page 68, lines 20-22. The sequence of AD10-7 was apparently determined from the isolated cDNA clone[1]. *See* WO 94/23756 at page 69, lines 22-25.

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[1]According to WO 94/23756, the nucleotide sequence of AD10-7 is depicted in "Fig. 16j." *See* WO 94/23756 at page 69, lines 22-25. The sequence shown in Fig. 16J of WO 94/23756, however, is labeled "AD3-4SP," while the sequence of AD7-10 is shown in Fig. 16R. It appears that the figures in WO 94/23756 do not correspond to the figure references found in the specification.

On the other hand, SEQ ID NO:1 of the present application was determined by screening *E. coli* colonies that had been transformed with an Alzheimer's disease cDNA library using polyclonal antibodies to human PTP. *See* Specification at page 33, lines 10-21. Restriction fragments were subcloned into pGem7 and then were sequenced. *See* Specification at page 33, line 21, through page 34, line 4. Thus, SEQ ID NO:1 and the sequence of AD10-7 set forth in WO 94/23756 were determined from distinct clones obtained by different screening methods. The differences between the sequences of AD10-7 and SEQ ID NO:1 are not necessarily due to errors in the sequencing process. Genetic differences in the source materials used to determine the sequences may be the cause of at least some of the differences. If so, it would have been impossible for a person of ordinary skill in the art to obtain SEQ ID NO:1 using the clone isolated in WO 94/23756.

Regardless of whether the material used to determine the two sequences is the same, Applicants note that a person of ordinary skill in the art would have had no reason to believe that the sequence information in WO 94/23756 contained errors. Thus, there would have been no motivation to determine the correct sequence even if such a determination were possible. Without knowledge of the correct nucleotide sequence, a person of ordinary skill in the art would have had no reason to produce antisense oligonucleotides, ribozymes, triple helix forming oligonucleotides or ribonucleotide external guide nucleic acid molecules that include nucleotide sequences that are complementary to or that correspond to sequences specifically located between nucleotides 150 and 1139 of SEQ ID NO:1 and that do not contain any of the positions of non-identity. In short, a skilled artisan would have relied upon the sequence information set forth in WO 94/23756. Thus, the existence of the alleged

"source of the correct sequence," *see* Paper No. 10, page 3, does not support a *prima facie* case of obviousness.

In view of the foregoing, Applicants respectfully request that the rejection of claims 17, 18, 20-30 and 32 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

III. Claim Objections

Claims 19 and 31 were objected to as being dependent upon a rejected base claim. *See* Paper No. 10, page 4. Applicants respectfully submit that the rejections of claims 17 and 30 (from which claims 19 and 31, respectively, depend) are in error. *See* discussion immediately above. Therefore, Applicants respectfully request that the objections to claims 19 and 31 be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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